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The Utility of fMRI for Assessing and Predicting Individual Differences in Fatigue Vulnerability

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14. ABSTRACT
Several studies have shown that fatigue from inadequate sleep is associated with serious performance decrements, increases in safety risks, and adverse health costs. Little has been done to explore the nature of individual differences in performance or the degree to which these differences can be predicted prior to sleep loss. The present study sought to replicate studies in which brain activation may identify those individuals who are susceptible to the effects of sleep deprivation. Following baseline cognitive testing and an fMRI, 11 participants underwent a complete sleep-deprivation study in which they were repeatedly given a battery of surveys and cognitive and mood tests at 2-hr intervals for 23 hours. Near the end of the 30-hr period, an additional fMRI examination identical to the first was performed for each participant. While in the scanner, participants took two cognitive tasks (Sternberg memory tasks and a binary detection task) and a magnetic resonance spectroscopy scan. The results indicated individuals who perform poorly during long hours of wakefulness may not have the cognitive reserve necessary to resist the effects of sleep deprivation. More research is necessary to determine whether fMRI can be a useful tool in identification of individuals who are resistant to the effects of long hours of wakefulness.

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Functional Magnetic Resonance Imaging; Magnetic Resonance Spectroscopy; Sleep deprivation; Fatigue

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SUMMARY

Several studies have shown that fatigue and sleepiness from inadequate sleep are associated with serious performance decrements, increases in safety risks, and adverse health costs. Decrements in performance of 25 to 30 percent have been shown to occur with every 24 hours of sleep loss. However, these results are based on average responses, and not individualized responses. Although it is known that there are wide differences in the response characteristics of fatigued individuals, little has been done to explore the nature of these differences or the degree to which these differences can be predicted prior to sleep loss. However, it is certainly clear that the averages of group responses to sleep deprivation do not accurately depict the impact of this stressor across all individuals. Thus, there are significant gaps in our knowledge associated with individual variations in fatigue susceptibility. Studies have shown that brain imaging (with fMRI) may offer a predictor of fatigue vulnerability. Data suggest baseline fMRI-scan activation during a working memory task may correlate with fatigue susceptibility. Such a finding would permit the use of fMRI as a selection factor or as a way in which fatigue countermeasures could be tailored to meet the needs of specific individuals. The present study sought to replicate previous studies in which brain activation, measured through fMRI, may identify those individuals who are susceptible to the effects of long hours of continuous wakefulness. A total of 11 individuals participated in the present study. Baseline cognitive testing and an fMRI were obtained for each participant. Over the next 23 hours, participants underwent a complete sleep-deprivation study in which they were repeatedly given a battery of surveys and cognitive and mood tests at 2-hr intervals. Near the end of the 30-hr period, an additional fMRI examination identical to the first was performed for each participant. While in the scanner (both pre- and post-sleep deprivation), participants took the two cognitive tasks (Sternberg memory tasks and the binary detection task) and lay quietly for a magnetic resonance spectroscopy scan (no cognitive tasks were presented during this scan). The results indicated that fMRI data can identify those individuals who are susceptible to the effects of sleep deprivation, supporting previous studies which suggest that individuals who perform poorly during long hours of wakefulness may not have the cognitive reserve necessary to resist the effects of a stressor such as sleep deprivation. It is clear that identification of individual variability in performance during sleep deprivation is still in an infancy stage and more research is necessary to determine whether fMRI can be a useful tool in identification of individuals who are resistant to the effects of long hours of wakefulness.

1.0 INTRODUCTION

Physiological responses to alertness and fatigue significantly affect how we interact with our daily environment and vary among individuals. Advances in technologies such as functional magnetic resonance imaging (fMRI) and magnetic resonance spectroscopy (MRS) are offering new opportunities to characterize the contributions of individual differences on the effects of sleep deprivation and counter-fatigue measures. We proposed to use fMRI and MRS as physiological functional measures with which to begin to assess the predictability of individual differences in fatigue resistance among healthy people. Follow-on research will be conducted in select populations such as pilots and others, but this initial effort primarily tested a more general subject pool.

The role of physiological differences between individuals in system effectiveness is becoming increasingly important in work environments. As systems become increasingly complex, organizations are expected to accomplish more tasks with fewer people – multi-tasking is becoming the norm in work environments. As organizations increase automation, redundancy in personnel is being continually reduced, and a single person is often in charge of multiple processes. For example, in the mid 20th century, 20 B-52 aircraft were required to destroy one bridge. Each aircraft had 5 crew members, resulting in a total of 100 people needed to accomplish the mission. Today, the same mission can be carried out by *one* highly sophisticated, $2 billion B-2 aircraft with a two-member crew. This example typifies the current job market. Jobs are increasingly being performed by fewer people operating highly automated, expensive equipment. To further exacerbate this problem, the pace and temporal organization of society's lifestyle often forces workers to perform in circadian-disrupted and/or sleep-deprived conditions. This compounded problem poses *serious* risk in safety-sensitive jobs.

Caldwell et al. (2005) and others have shown that fatigue and sleepiness from inadequate sleep are associated with serious performance decrements (Caldwell, Caldwell, Brown & Smith, 2004; Dement & Vaughn, 1999), increases in safety risks (Dinges, 1995; Leger, 1994; Mitler et al., 1988; Webb, 1995), and adverse health costs (Briones et al., 1996; Buysse & Ganguli, 2002). Decrements in performance of 25 to 30 percent have been shown to occur with every 24 hours of sleep loss (Angus & Heslegrave, 1985; Belenky et al., 1994). However, these results are based on average responses, and not individualized responses. Although it is known that there are wide differences in the response characteristics of fatigued individuals (Balkin et al., 2000; Caldwell et al., 2004; Caldwell et al., 2005; Morgan, Winne & Dugan, 1980; Tyler, 1965; Van Dongen, Baynard, Nosker & Dinges, 2002; Van Dongen, Maislin, Mullington & Dinges, 2003), little has been done to explore the nature of these differences or the degree to which these differences can be predicted prior to sleep loss. However, it is certainly clear that the averages of group responses to sleep deprivation do not accurately depict the impact of this stressor across all individuals. Thus, there are significant gaps in our knowledge associated with individual variations in fatigue susceptibility.

Recent advances in technology and research are providing exciting insights into the need for better understanding of differences in brain functioning across individuals. For years, imaging technologies have offered specific capabilities to understanding brain activities. In particular,

MRI is useful for volumetric characterization of brain regions, fMRI is useful for mapping brain function, and MRS provides information on tissue composition and chemical makeup *in vivo*. However, of even greater interest for the present study is the finding by Caldwell et al. (2005) that brain imaging (with fMRI) may offer a predictor of fatigue vulnerability. In the Caldwell et al. (2005) study, non-sleep-deprived fMRI data from 7 Air Force pilots were shown to correlate with sleep-deprived flight simulator performance data taken during 37 hours of continuous wakefulness; pilots who showed the most overall cortical activation in the non-deprived state also showed the least impairment in performance after being subjected to at least 37 hours of continuous wakefulness. Mu et al. (2005a) also demonstrated with fMRI that it was possible to predict fatigue susceptibility from volunteers known to commonly encounter job-related sleep loss. Mu and colleagues conducted a study in which 33 participants underwent fMRI scanning during the performance of the Sternberg Working Memory Test (SWMT) in the morning after a normal night of sleep and again after 30 hours of continuous wakefulness. Based on reaction time (RT) scores from the SWMT after 30 hours awake, 10 participants were classified as fatigue resistant (their RTs were shorter after 30 hours wake than during their rested, baseline performance), and 10 participants were classified as fatigue vulnerable (their RTs were longer after 30 hours awake than during their rested, baseline performance). The results indicated that the individuals in the fatigue-resistant group had significantly more brain activation than did the fatigue-vulnerable group, suggesting that brain activation may be useful in differentiating individuals vulnerability to the effects of sleep deprivation.

Data from these limited studies suggest baseline fMRI-scan activation during a working memory task may correlate with fatigue susceptibility. Such a finding would permit the use of fMRI as a selection factor or as a way in which fatigue countermeasures could be tailored to meet the needs of specific individuals. However, further investigation of the findings from Caldwell et al. and Mu et al. are needed to fully understand and validate the initial research efforts and conclusions. Other recent studies have begun to investigate the relationship between cerebral metabolites, such as N-acetyl-aspartate (NAA), choline (CHO), creatine (CRE), lipids (LIP) and lactate (LAC), and the mechanisms of vulnerability to fatigue. In Puri et al. (2002) it was shown that the CHO/CRE ratio is elevated in the occipital lobes of chronic fatigue syndrome patients relative to healthy subjects. The same study also found that chronic fatigue syndrome patients had a relatively even distribution of choline throughout the brain whereas healthy controls had significantly different levels of choline in the motor cortex compared with the occipital lobe. Urrila et al. (2006) performed a study of 8 women who underwent MRS before and after a period of 40hrs of sleep deprivation. They found that NAA and CHO in the occipital lobe decreased with sleep deprivation. The study did not included psychomotor vigilance testing and thus the predictive power of the initial baseline MRS scans was not investigated. These preliminary studies suggest that MRS may be useful modality in the study of the neural mechanisms of sleep deprivation-induced fatigue.

2.0 METHOD, ASSUMPTION AND PROCEDURES

2.1 Equipment and facilities

All MRI procedures used a Siemens MAGNETOM Avanto 1.5T scanner using a 12-channel bird-cage head coil. The scanner was located at the Innovation Center at Kettering Health Network. Vigilance testing used a dedicated Psychomotor Vigilance Testing device (the PVT-192). CANTABeclipse testing was conducted via a standard laptop computer outfitted with touchscreen technology. The Rapid Decision Making task was performed on a standard desktop computer and the participant responded with a 3-button mouse. Subjective scales consisted of locally constructed paper-and-pencil questionnaires (visual analog scales) and the Profile of Mood States (POMS). Wrist activity data were acquired using wrist-worn monitors from Ambulatory Monitoring, Inc.

2.1.1 Sternberg Working Memory Task. During the fMRI scans, short-term memory was assessed via the Sternberg Working Memory Task (SWMT). This test has been widely used and validated (Rypma & D'Esposito, 1999; Rypma, Prabhakaran, Desmond, Glover, & Bagrieli, 1999; Veltman, Rombouts, & Dolan, 2003) and is known to be sensitive to the effects of sleep deprivation (Elkin & Murray, 1974; Polzella, 1975). During the SWMT, participants were asked to judge whether a test letter is contained in a previously-memorized short sequence of letters. Reaction times (RTs) and percent correct were recorded. The participants were presented with random sets of 1, 3, or 5 letters as a "recognition" set. Following a blank screen which represented a "retention" period, the participants were expected to recall whether or not a test letter was present within the recognition set. The SWMT lasted for 6 min, 24 s, not including a control task. Reaction times and accuracy were recorded for analyses.

2.1.2 Implementation of the SWMT in the fMRI scanner. In order for the SWMT to be performed during the fMRI scan, it was modified to fit an imaging design and to enable the acquisition of behavioral data within the scanner. Briefly, each functional scan consisted of 12 blocks. Each block included a control task (32 s) with an alternative Sternberg task (32 s). Each task contained two trials, with each trial lasting 16 s. The entire functional scan lasted approximately 12 min, 48 s. Visual stimuli were projected from an MR-compatible video projector (Psychology Software Tools, Pittsburgh, PA) to a mirror located at the top of a 12-channel bird-cage head coil. User input was monitored using hand clickers. Participants were instructed to respond with their index fingers (left or right) to "YES" or "NO" (this order was randomized between individuals). The control trial consisted of a 3-s viewing of 6 asterisks in 2 rows, followed by a 7-s delay, and then a 3-s viewing of either "YES" or "NO" presented at the center of the screen. During the control trial, each participant was asked to press the appropriate button for "Yes" or "No" when "YES" or "NO" was presented on the viewing mirror in a randomized order. During the SWMT trial, arrays of either 1, 3, or 5 letters were randomized to display on the viewing mirror. Participants viewed the set of letters for 3 s (recognition). They then maintained this set in mind during a 7-s delay (retention). Subsequently, a probe letter was presented on the screen for 3 s, and participants responded either "YES" or "NO" according to whether the probe letter was included in the previously viewed set (recall). There was a 1.5-s time-out interval (rest) following presentation of the probe and another 1.5-s time-out interval

before the display of the "recognition" letter(s). Participants were instructed to respond as accurately as possible. The sequence of presentation is presented in Figure 1 below.

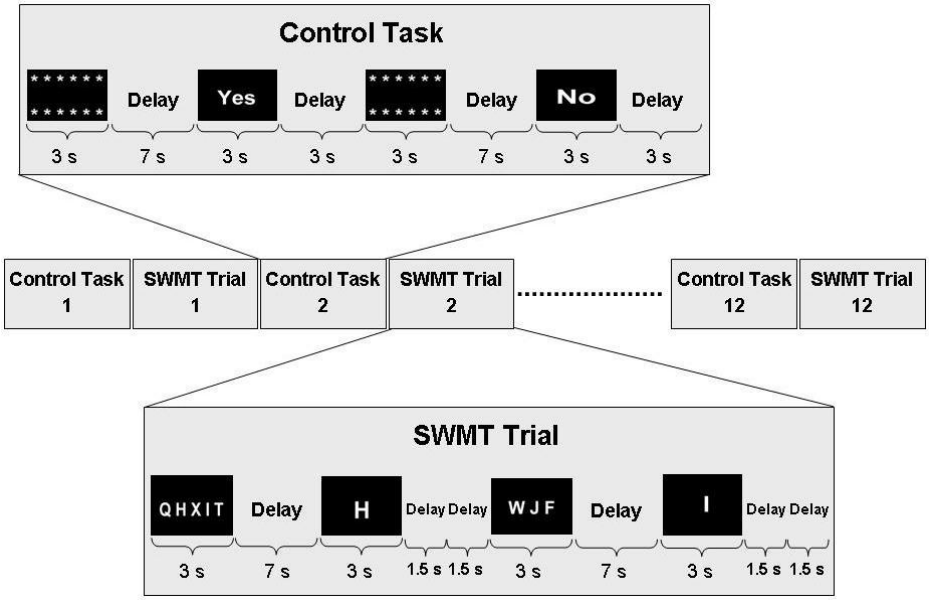

Figure 1. Sequence of control and trial displays for the Sternberg Working Memory Test (SWMT) presented during the MRI scan.

The fMRI images were obtained with standard procedures. First, a set of 160 contiguous axial high-resolution anatomical images was acquired in an ascending fashion using the following parameters: TR = 1900 ms, TE = 3.37 ms, slice thickness = 1 mm, in-plane pixel size = 1 x 1 mm^2, field of view (FOV) = 25.6 cm, image matrix = 256 x 256. Next, a set of T1-weighted axial low-resolution anatomical images encompassing the whole brain was acquired in an interleaved fashion using the following parameters: TR = 663 ms, TE = 17 ms, slice thickness = 6 mm, interslice gap = 1 mm, in-plane pixel size = 0.5 x 0.5 mm^2, FOV = 25.6 cm, number of slices = 24, image matrix = 512 x 512.

2.1.3 Binary detection task (BDT). During the fMRI scans, attention, cognitive speed, and vigilance were tested using a binary detection task (BDT). The participants were shown an image with red circles and blue squares which may or may not contain a blue circle hidden somewhere in the picture (Figure 2). The participants were expected to decide whether or not the picture contained a blue circle. Their accuracy and reaction time were recorded for analyses. The binary detection task lasted 3 min, 24 s without a control task.

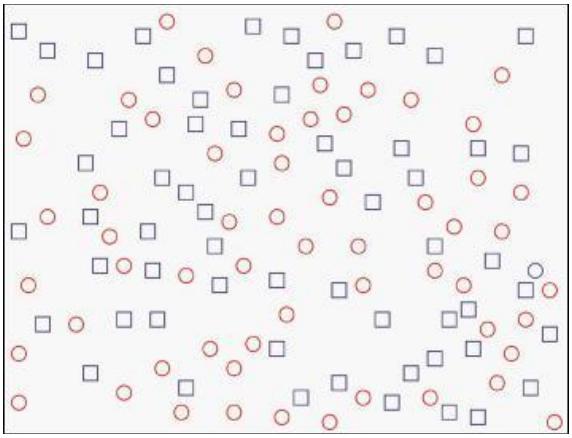

Figure 2. Binary detection task (BDT) sample image.

2.1.4 Implementation of the binary detection task in the fMRI scanner. The implementation of the binary detection task inside the fMRI scanner used the same block design and "YES" or "NO" hand-pads as the implementation of the SWMT. The control trial consisted of a 6.5-s viewing of a baseline picture, which contained Kettering Health Network logo, and then a 1.5-s viewing of either "YES" or "NO" presented at the center of the screen. During the control trial, each participant was asked to press the appropriate button for "Yes" or "No" when "YES" or "NO" was presented on the viewing mirror in a randomized order. During the binary detection task trial, a picture with red circles and blue squares, which may or may not have a blue circle, was displayed for 6.5 s. The participant was instructed to respond "YES" or "NO" regarding whether they believed the picture contained the blue circle. Participants were instructed to respond as fast and as accurately as possible. The sequence of control and test screens is shown in Figure 3.

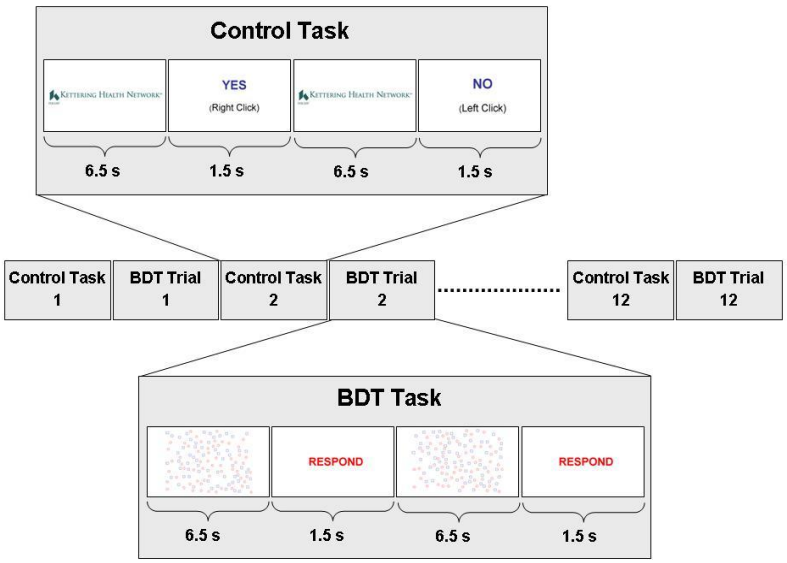

Figure 3. Sequence of control and trial displays for the binary detection task (BDT) presented during the MRI scan.

The fMRI images were obtained during the BDT in the same manner as during the SWMT. The parameters to acquire the set of images were the same as described above.

2.1.5 Magnetic Resonance Spectroscopy (MRS). Multi-voxel magnetic resonance spectroscopy (MRS) was used to identify and evaluate levels of various metabolites in the brain (choline, lactate, creatine, N-Acetyl Asparatate, and lipids). Spectral analysis was performed on specific regions of the brain that are involved with working memory, primarily the frontoparietal network that is involved with verbal working memory processing, anterior cingulated, and thalamus.

2.1.6 Implementation of MRS in the MR scanner. The implementation of MRS did not require that the participant engage in any cognitive activity. The participant was instructed to lay as still as possible during the acquisition to minimize motion-related discrepancies in the data. The data acquired was then processed to plot and identify metabolite peaks. The MRS sequence took from 3 to 6 min.

Magnetic resonance spectroscopy data were obtained using a multi-voxel PRESS pulse sequence on two volumes of interest (VOI) of 16 x 16 x 8 voxels (voxel size = 7.6 x 7.5 x 12.5 mm^3) using the following parameters: TR = 1500 ms, TE = 135 ms, number of averages = 4, flip angle = 90^o, and water suppression bandwidth = 35 Hz. The first VOI was positioned to acquire data from the putamen, globus pallidus, and occipital lobe while the second was positioned to acquire from the pons (Figure 4).

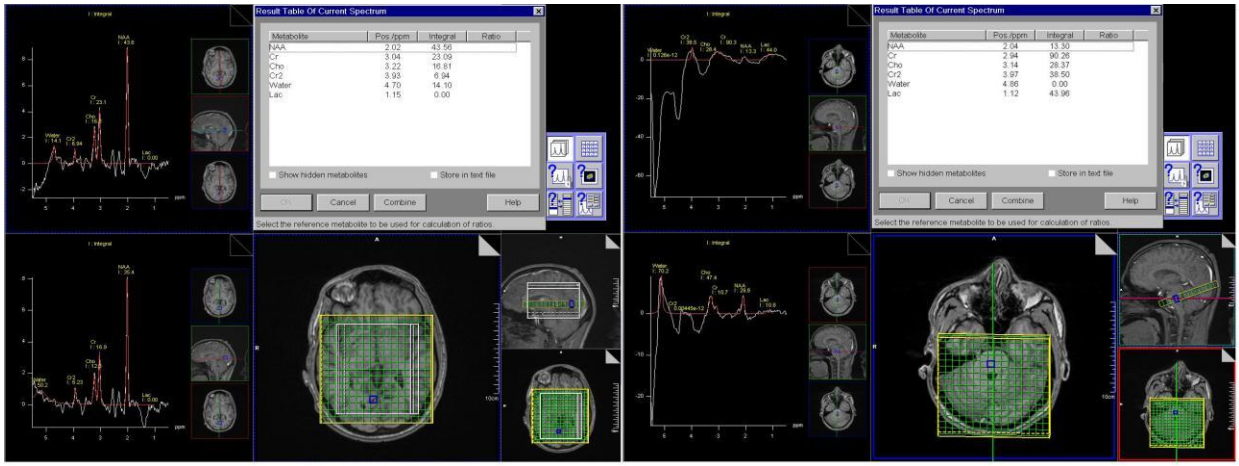

Figure 4. Examples of volumes of interest for putamen, globus pallidus, occipital lobe, and pons.

2.1.7 Psychomotor Vigilance Test. Vigilance performance was assessed using the Psychomotor Vigilance Task (PVT), a portable simple reaction time test known to be sensitive to sleep loss (Dinges et al., 1997). The PVT requires sustained attention and discrete motor responses. The 8" x 4.5" x 2.4" portable, battery-operated device visually displays numbers counted up by milliseconds in a window. The stimulus is presented for up to 1 min (60,000 msec), allowing the participant to respond. The participant presses a microswitch which allows reaction time to the stimulus to be recorded. The interstimulus interval varies randomly from 2 to 12 s. The data were stored on computer and reduced by custom software for future analysis.

2.1.8 Cambridge Neuropsychological Assessment Battery: Eclipse (CANTABeclipse). The CANTABeclipse is a battery of 22 tests which are sensitive to cognitive changes caused by a wide range of central nervous system disorders and medication effects (Lowe & Rabbitt, 1998; Randall, Fleck, Shneerson & File, 2004). These tests are divided into six main types of tasks: 1) training and screening; 2) decision making and response control; 3) visual memory; 4) executive function, working memory and planning; 5) attention; and 6) semantic/verbal memory. All tests are administered by computer using a touch screen for subject responses. A subset of these tests was selected to specifically investigate the higher order cognitive functions of planning, decision making, and visual-spatial memory. The selected four tests are described below.

1) The *Spatial Recognition Memory* test is a two-choice forced discrimination paradigm in which the participant is presented with a white square which appears in sequence at five different locations on the screen. In the recognition phase, the participant sees a series of five pairs of squares, one of which is in a place previously seen in the presentation phase. The other square is in a location not seen in the presentation phase. Locations are tested in the reverse of the presentation order. This sub-test is repeated three more times, each time with five new locations. This task took approximately 5 min to complete and was presented twice.

2) The *Spatial Working Memory* task is a test of the participant's ability to retain spatial information and to manipulate remembered items in working memory. The test began with a number of colored squares shown on the screen. The goal of this test was that, by a process of elimination, the participant would find a blue "token" in each of a number of boxes and use them to fill up an empty column on the right hand side of the screen. The number of boxes was gradually increased from three to eight boxes. The color and position of the boxes used were changed from trial to trial to discourage the use of stereotyped search strategies. This task took approximately 10 min.

3) *Stockings of Cambridge* is a test of spatial planning based upon the Tower of London test. The participant was shown two displays containing three colored balls. The displays can easily be perceived as stacks of colored balls held in stockings or socks suspended from a beam. The rules involved 3-D concepts which fit with verbal instructions. The participant must use the balls in the lower display to copy the pattern shown in the upper one. Administration time was approximately 10 min.

4) The *Cambridge Gambling Task* assesses risk-taking and decision-making behavior outside a learning environment. On each trial, the participant was presented with a row of 10 boxes across the top of the screen, some of which were red and some of which were blue. At the bottom of the screen were rectangles containing the words 'Red' and 'Blue'. The participant guessed whether a yellow token was hidden in a red box or a blue box. In the gambling stages, participants started with a number of points, displayed on the screen, and selected a proportion of these points, displayed in either rising or falling order, in a second box on the screen, to gamble on their confidence in this judgment. A stake box on the screen displayed the current amount of the bet. The participant tried to accumulate as many points as possible.

2.1.9 Rapid Decision Making test. The Rapid Decision Making test requires one to assess the threat of a situation based on multiple dimensions and to react quickly based on this assessment. From the highest commander to the lowest ranking soldier, the battlefield imposes intrinsic limitations on the quality of information received. Decisions and actions must take place rapidly under uncertainty concerning multiple factors (e.g., enemy movements, positions, capabilities, and intentions compound with conditions of smoke, geography, and deliberate confusion from the enemy). The Rapid Decision Making test replicates the situation where the soldier must select approaching enemy targets among uncertain targets (questionable civilians) and friendlies, while also assessing their levels of threat based on proximity.

2.1.10 POMS and VAS. Subjective evaluations of mood were made with the Profile of Mood States (POMS) (McNair, Lorr, & Droppleman, 1981). The POMS is a 65-item questionnaire which measures affect or mood on 6 scales: 1) tension-anxiety, 2) depression-dejection, 3) anger-hostility, 4) vigor-activity, 5) fatigue-inertia, and 6) confusion-bewilderment. Subjective sleepiness/alertness was measured via the Visual Analog Scale (VAS) (Penetar et al., 1993). This questionnaire consists of several 100 mm lines; at each end of the lines are opposite adjectives such as "not at all" and "extremely," and centered under each line are the adjectives "alert/able to concentrate", "anxious", "energetic", "feel confident," "irritable," "jittery/nervous", "sleepy," and "talkative." The participant was required to indicate the point on the line which corresponded to how he felt along the continuum. The answer was scored by measuring, in

millimeters, where the responses fell on each of the lines. Administration and scoring of both POMS and VAS were computerized.

2.1.11 WAM (Wrist activity monitors). Wrist monitors (Ambulatory Monitoring, Inc) were used to track sleep/activity rhythms in a relatively unobtrusive fashion. In this study, the WAMs (which are battery-powered devices about the size of a wrist watch) were used to ensure that participants obtained adequate sleep prior to the time at which they reported to the Laboratory for testing. Activity data were downloaded once the participant arrived at the Laboratory (prior to the sleep-deprivation period), and computer-generated actigraphs were visually inspected to ensure compliance with experimental instructions.

2.2 Participants

Military personnel between the ages of 25 and 45 were recruited to participate in the present sleep deprivation/imaging study. Participants were recruited locally from military bases, primarily from Wright-Patterson Air Force Base (WPAFB), OH, and various National Guard units and other bases around the country. The information located on the "Information Brief" (Appendix C) was used as the text body for emails distributed to potential volunteers. Men and women were targeted to best represent the population of active duty U.S. Air Force personnel. Compensation was not provided to any participant; however, travel expenses were paid by the Air Force Research Laboratory (AFRL) to those volunteers traveling from outside the WPAFB area. All military members were on duty during their participation in this study.

All participants were subjected to an abbreviated physical examination to determine that they were free from significant health problems. Also, participants were screened for medication use which may impact the validity of the results (Appendix A). Pregnancy tests were conducted prior to entry into the study for the female participant.

2.3 Description of study

2.3.1 Data collection: Prior to testing, participants wore a wrist activity monitor (WAM) for 3 days and nights to ensure proper sleep patterns prior to the study. WAMs were distributed to each participant 3 days prior to actual testing. During an initial visit, participants were trained on the cognitive batteries. On the first day of actual testing, participants arrived at approximately 0930; baseline testing began at 1000 and took approximately 1.25 hours. At 1200, an MRI examination including high-resolution anatomical imaging, fMRI, and MRS, was taken for each participant. Over the next 23 hours, participants were housed and tested in a laboratory facility located at the Innovation Center by AFRL and University of Dayton Research Institute (UDRI) personnel. During this time, they underwent a complete sleep-deprivation study in which they were repeatedly given a battery of surveys and cognitive and mood tests which include the psychomotor vigilance test (PVT, a 10-min reaction-time evaluation), the CANTABeclipse (spatial scanning, spatial working memory, planning and problem solving, risk-taking task), Rapid Decision Task, and VAS and POMS (measuring sleepiness, alertness, concentration, and other dimensions). Testing occurred at 2-hr intervals. The initial session was considered

baseline data. Subsequent sessions collected fatigue-related performance, subjective, and physiological data. Near the end of the 30-hr period, an additional MRI examination identical to the first was performed for each participant. While in the scanner (both pre- and post-sleep deprivation), participants took the two cognitive tasks (Sternberg memory tasks and the binary detection task) and lay quietly for a magnetic resonance spectroscopy scan (no cognitive tasks were presented during this scan). A schedule of the entire testing period is shown in Table 1.

Table 1. Daily testing schedule

	Time	Event
	0600	Wake-up time for participant
	0930	Arrival of participant at lab
Baseline	1000	Cognitive Tests
		Lunch
	1200	Pre-deprivation fMRI
Session 1	1300	Cognitive Tests
Session 2	1500	Cognitive Tests
Session 3	1700	Cognitive Tests
Session 4	1900	Cognitive Tests
Session 5	2100	Cognitive Tests
Session 6	2300	Cognitive Tests
Session 7	0100	Cognitive Tests
Session 8	0300	Cognitive Tests
Session 9	0500	Cognitive Tests
Session 10	0700	Cognitive Tests
Session 11	0900	Cognitive Tests
Session 12	1100	Cognitive Tests
	1230	Post-deprivation fMRI

Time	Cognitive Tests
00	Profile of Mood States (POMS)/Visual Analogue Scales (VAS)/Psychomotor Vigilance Test (PVT)
20	Rapid Decision-making Test
30	Cambridge Neuropsychological Assessment Battery (CANTAB) (Spatial Recognition Memory, Spatial Working Memory, Stockings of Cambridge, Cambridge Gambling Task)

3.0 RESULTS AND DISCUSSION

A total of 11 individuals (10 men and 1 woman, mean age was 31.60, standard deviation of 4.43) participated in the study. One man did not complete the entire study, leaving 10 complete data sets. The wrist activity monitor was used to determine compliance with the sleep requirement that at least 7 hours of sleep occur for 3 nights prior to the beginning of the continuous wakefulness period. All participants fulfilled the requirement except for two. Upon questioning one of the participant's sleep behavior, it was determined that he normally slept for 6 to 6.5 hours, even on weekends and holidays, and was not able to sleep the required 7 hours. He was therefore allowed to continue participation in the full study since it was determined that he was probably a "short sleeper." The other individual who did not sleep as instructed obtained over 8 hours of sleep the night prior to his test days, so he was allowed to enter the study. All 10 individuals' data were analyzed for the performance tests during the wake period. One man was left-handed and was not included in fMRI data analysis.

For each of the cognitive tasks, a baseline-adjusted score was calculated (difference score = session score – baseline score) to give a difference score for each session. The difference scores for each of the cognitive tasks were analyzed with a repeated measures analysis of variance (ANOVA), with session as the repeated factor. The alpha level was set at .05. Huynh-Feldt adjusted degrees of freedom were used if the sphericity assumption was not met. Significant session main effects were further analyzed for differences between means.

Functional MRI processing was carried out using the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL, Analysis Group, FMRIB, Oxford, UK). Functional data were first motion-corrected by registering all volumes to a reference volume by minimizing a correlation ratio term with motion described by a 6-parameter rigid body model. The functional data were then skull stripped, spatially smoothed with a Gaussian convolution of Full-Width Half-Maximum (FWHM) equal to 5 mm, and temporally smoothed with a high pass filter of cutoff frequency equal to 100 Hz. A boxcar paradigm with alternating rest and task periods was used to process both the SWMT and BDT datasets. Processing of the SWMT acquisitions used a rest period of 32s and a task period of 32s. Processing of the BDT acquisitions used a rest period of 16s and a task period of 16s.

The block design was then convolved with a hemodynamic response function to approximate the activation patterns. Activation and deactivation maps were then created using the General Linear Model with one explanatory variable and two contrasts with weights [1 0] and [-1 0]. The resulting z-maps were corrected for family-wise error rates using a clustering method where contiguous voxels with a z-value of 2.3 or greater were considered a cluster. The significance of each cluster was then estimated from Gaussian random field theory. Clusters with a *p*-value of .05 or less were considered significant.

The activation data were then registered to the MNI152_T1_2mm_brain atlas. For the SWMT results, regions-of-interests (ROIs) defined by the MNI152 atlas along with a z-threshold of 2.3 were used for calculation of global activation and deactivation, as well as activation in the left dorsolateral prefrontal cortex (LDLPFC), left posterior parietal cortex (LPPC), and the left

ventrolateral prefrontal cortex (LVLPFC). These areas correspond to those believed to be used in verbal working memory (Caldwell et al., 2005).

Because the BDT has not previously been used as an fMRI stimulus, we developed ROI's based on the average of BDT activation for 9 healthy, right-handed volunteers. This resulted in seven ROI's: 1) the frontal and limbic portions of Brodmann area 32 (Figure 5A); 2) Brodmann area 6 (Figure 5B); 3) the inferior frontal gyrus, aka Broca's area (Figure 5C); 4) Brodmann area 7 (Figure 5D); 5) the fusiform gyrus (Figure 5E); 6) Brodmann area 19 (Figure 5F); and 7) the entire cerebellum (Figure 5G).

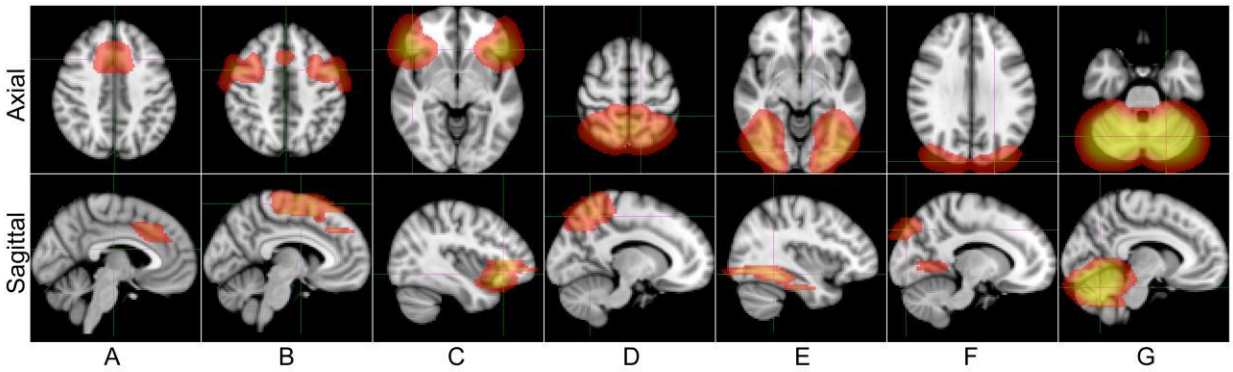

Figure 5. Axial (top row) and sagittal (bottom row) regions of interest for BDT analysis

The resulting values for the activated voxels in the ROI's were used in the various analyses. Correlations between the activated voxels obtained from the Sternberg Working Memory task and the performance data from the Spatial Working Memory task were calculated. In addition, correlations between the activated voxels obtained from the Binary Detection task and the performance data from the Spatial Recognition Memory task were calculated.

The acquired MRS data were processed using the Siemens MR Spectroscopy Evaluation Task Card. Post-processing steps included filtering, Fourier transformation, frequency shifting, and phase correction. A Gaussian function was used to fit the resulting spectra, and the area-under-the-curve (AUC) for the five primary metabolites (choline - CHO, lactate - LAC, creatine - CRE, N-Acetyl Asparatate – NAA, and lipids) was determined. The AUC was then used to create maps of metabolite concentration throughout the brain for each metabolite and each participant. Finally, the total concentrations of NAA, CHO, LAC, and CRE were computed in the basal ganglia (BG), pons, and occipital lobe for each participant before and after sleep deprivation and correlated with the results of the SWMT.

3.1 Psychomotor Vigilance Task (PVT)

The metrics obtained and analyzed for the PVT were mean reaction time (RT), the 10% fastest reaction times (FRT), the 10% slowest reaction times (SRT), and lapses. Reaction times were

transformed to the reciprocal in order to normalize the data for the repeated measures analysis of variance.

A significant effect for session was found for RT ($F(11, 99) = 22.69$, $p<.001$), FRT ($F(11, 99) = 18.403$, $p<.001$), SRT ($F(11, 99) = 22.806$, $p<.001$), and lapses ($F(11, 99) = 9.046$, $p<.001$). All reaction time metrics revealed both linear and cubic trends; lapses only revealed a linear trend. Figure 6 illustrates the session effect for each of the variables.

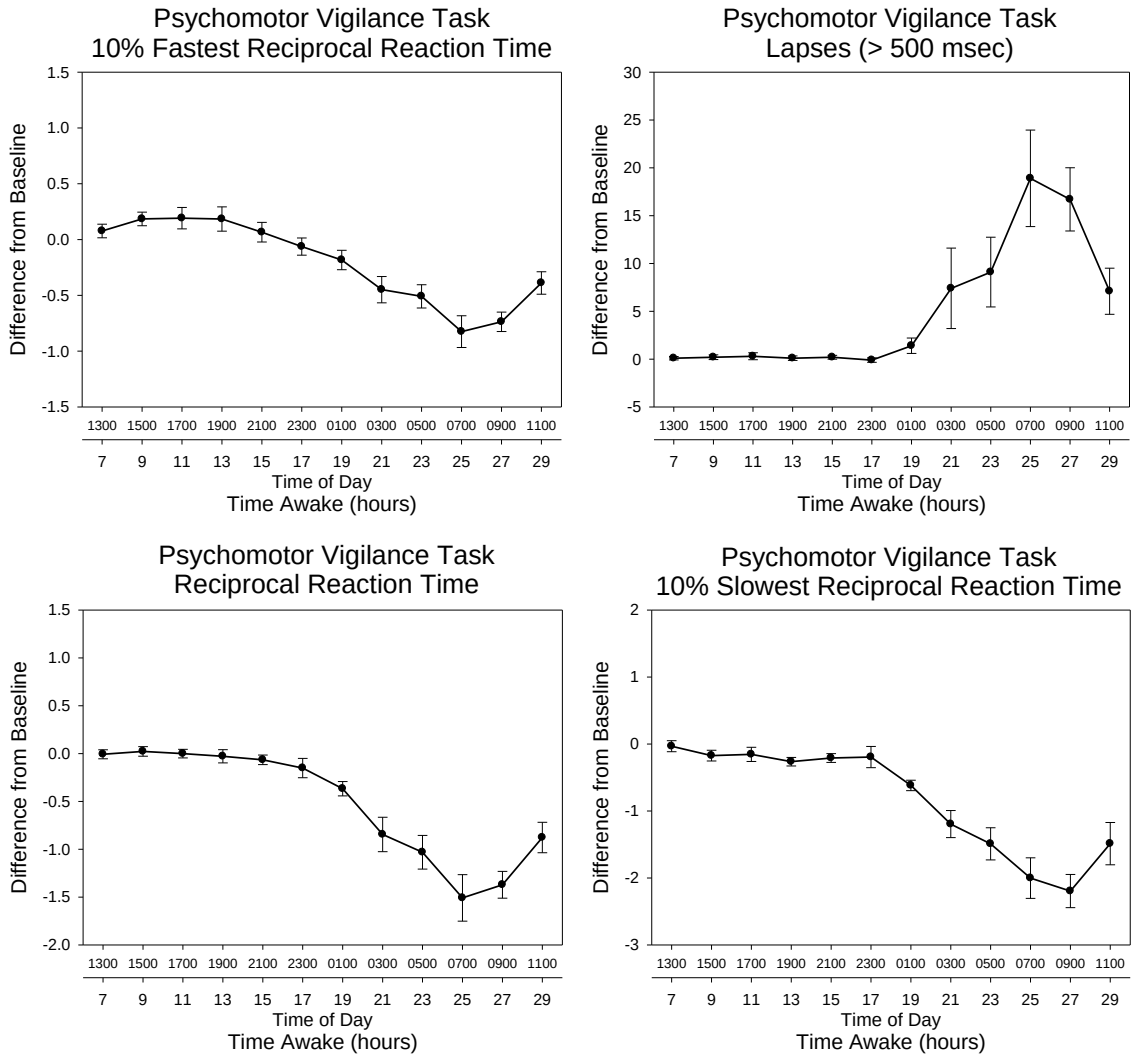

Figure 6. Session effects for PVT metrics RT, FRT, SRT, and lapses (means with sd)

3.2 Cambridge Neuropsychological Assessment Battery: Eclipse (CANTABeclipse)

Each of the subtests of the CANTABeclipse was analyzed separately. The results are presented below.

1) The *Spatial Recognition Memory* task metrics were percentage of correct trials and average correct latency (speed of participant's response). The ANOVA revealed a significant session effect for percent correct ($F(11, 99) = 2.886$, $p<=.002$), but not for correct latency ($p>.05$). Further analyses for percent correct indicated a linear trend ($p = .010$). The effect is illustrated in Figure 7.

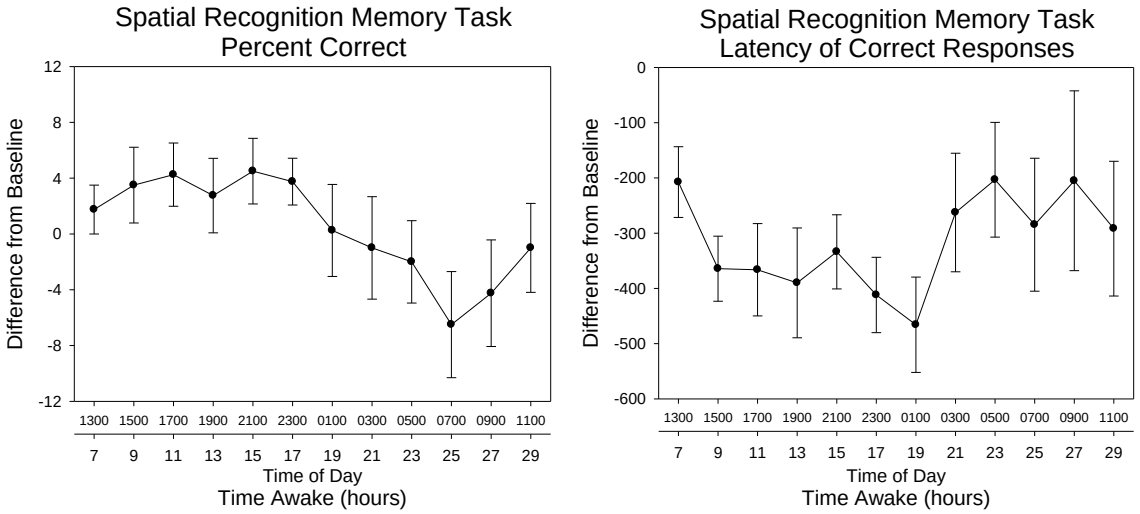

Figure 7. Session effect for Spatial Recognition Memory task (means with sd).

2) The *Spatial Working Memory* task metrics included total between errors, total search time, and strategy which were analyzed with a one-way ANOVA, with session as the repeated factor. A 2-way ANOVA also was calculated for between errors and search time with difficulty (size of box) and session as the repeated factors. The one-way ANOVA revealed significant session effects for total between errors ($F(11, 99) = 3.547$, $p<.001$) and strategy ($F(11, 99) = 4.361$, $p<.001$), but not for total search time ($p>.05$). The effects of session are illustrated in Figure 8. The 2-way ANOVA revealed a significant interaction between difficulty and session for between errors ($F(22, 198) = 2.471$, $p<.001$), but not for mean search time ($p>.05$). Further analyses indicated a session effect for the 6-box and 8-box levels of difficulty ($F(11,99) = 2.003$, $p=.036$; $F(11,99) = 3.235$, $p=.001$, respectively), but not for the 4-box level ($p>.05$). The interaction effects are illustrated in Figure 9.

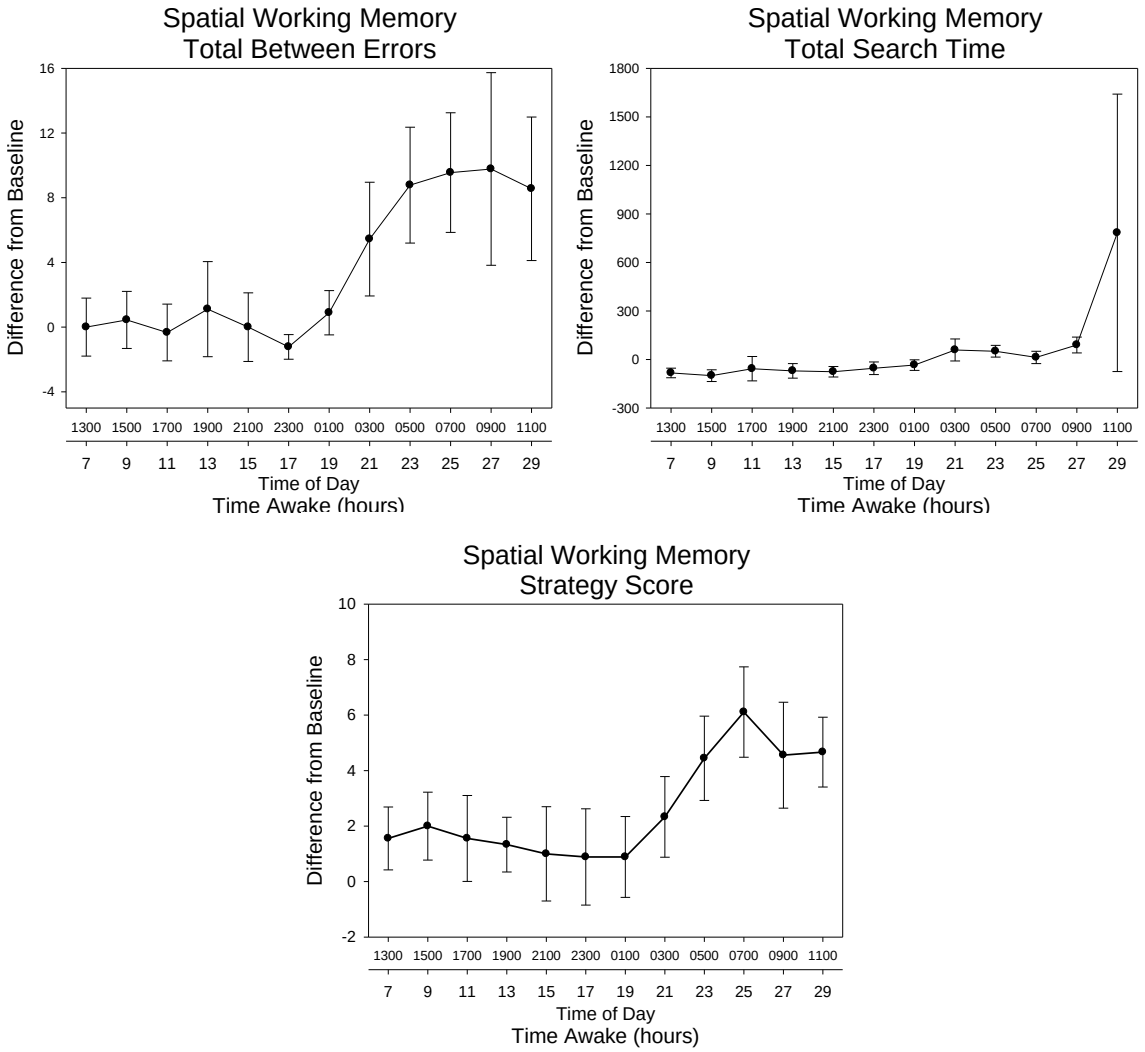

Figure 8. Spatial Working Memory task session effects (mean and sd)

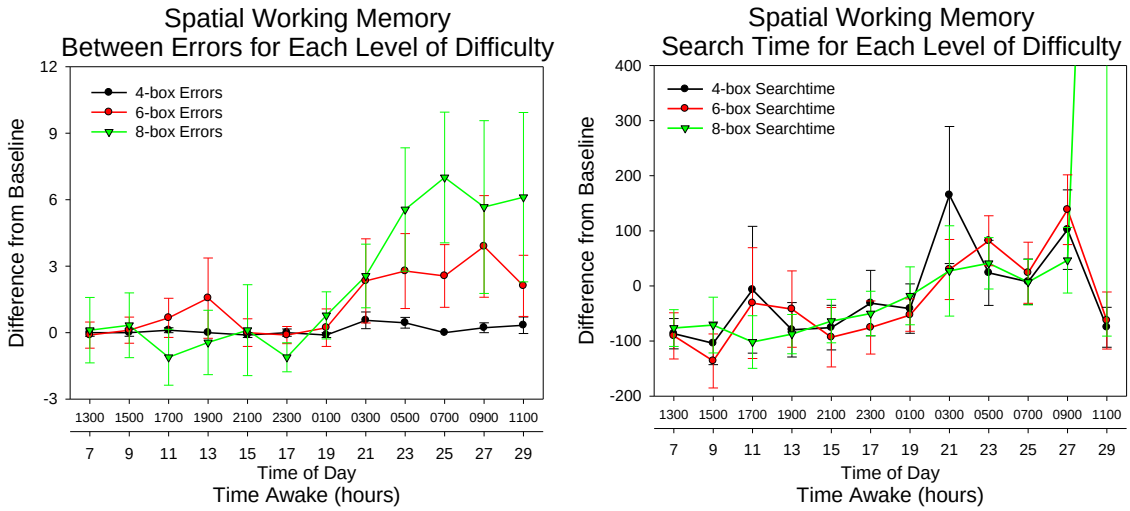

Figure 9. Spatial Working Memory task interaction effects between session and difficulty level (mean and sd)

3) The *Stockings of Cambridge* task metrics included initial search time, mean thinking time, and strategy score. The repeated measures ANOVA did not reveal any significant session effect for any of the metrics (p>,05).

4) The *Cambridge Gambling Task* metrics included delay aversion, deliberation time, quality of decision, risk adjustment, and risk taking scores. The ANOVA indicated significant session effects for delay aversion ($F(11, 99) = 5.512$, $p < .001$), quality of decision ($F(11, 99) = 2.185$, $p = .021$), risk adjustment ($F(11, 99) = 2.521$, $p = .008$), and risk taking ($F(11, 99) = 2.646$, $p = .005$). Deliberation time and the overall bet did not significantly differ across the sessions ($p > .05$). Delay aversion and risk adjustment revealed linear trends ($p < .01$, $p < .05$ respectively). Quality of decision making revealed a cubic trend, but not a linear trend ($p < .05$). Risk taking showed a tendency toward a quadratic trend ($p = .062$). Figure 10 illustrates the session effects for all the metrics.

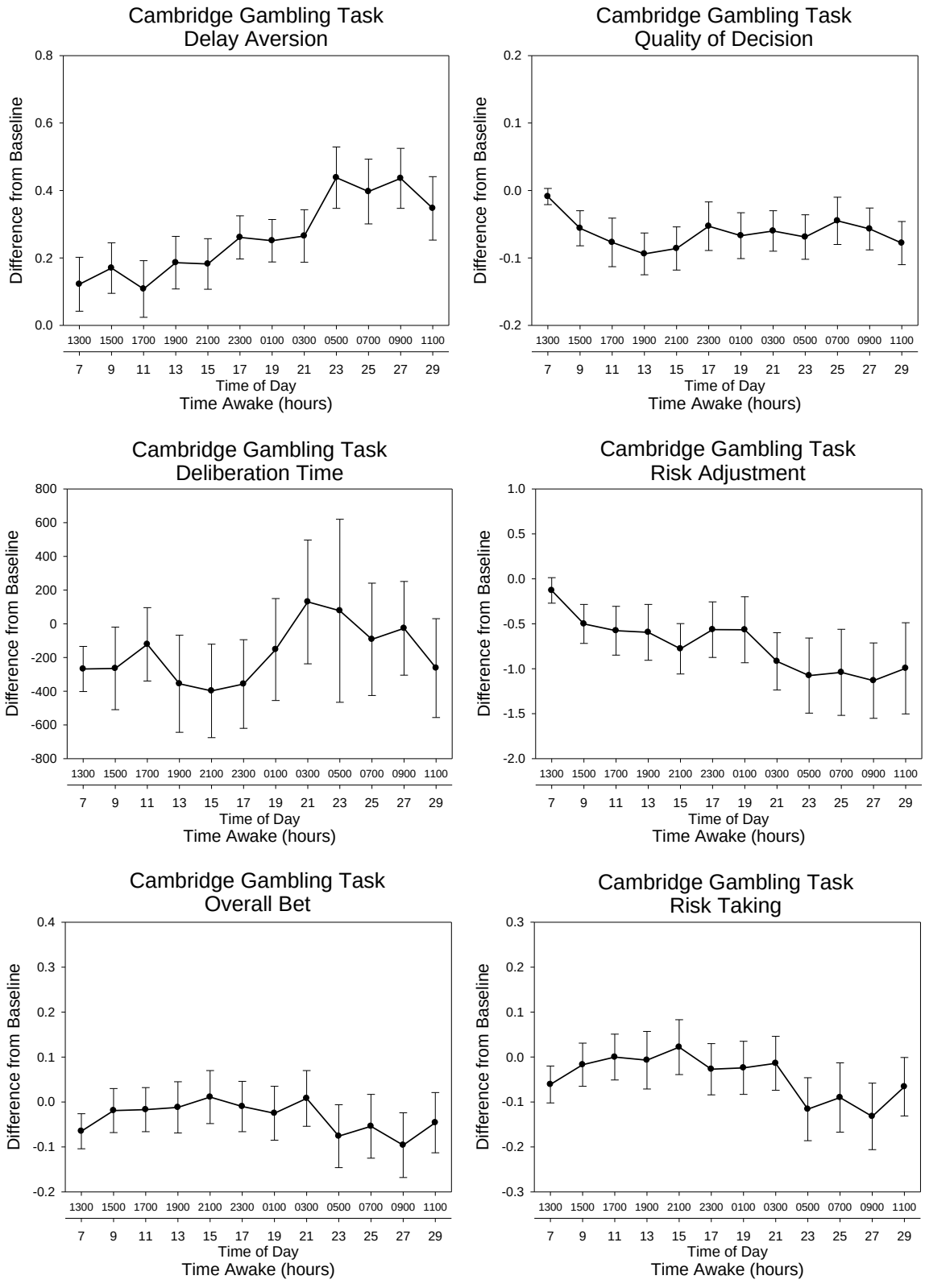

Figure 10. Session effects for Cambridge Gambling Task (means and sd)

3.3 Rapid Decision Making Task

The metrics analyzed for the Rapid Decision Making Task were percent correct, RT for hits, and RT for hits standard deviation. The ANOVA for these metrics indicated a significant session effect for RT for hits ($F(11,99) = 9.519$, $p < .001$), and RT for hits standard deviation ($F(11,99) = 10.271$, $p < .001$), but not for percent correct ($p>.05$). Follow-up analyses on both RT for hits and the standard deviation for RT hits indicated significant linear and cubic trends ($p>.05$). These effects are illustrated in Figure 11.

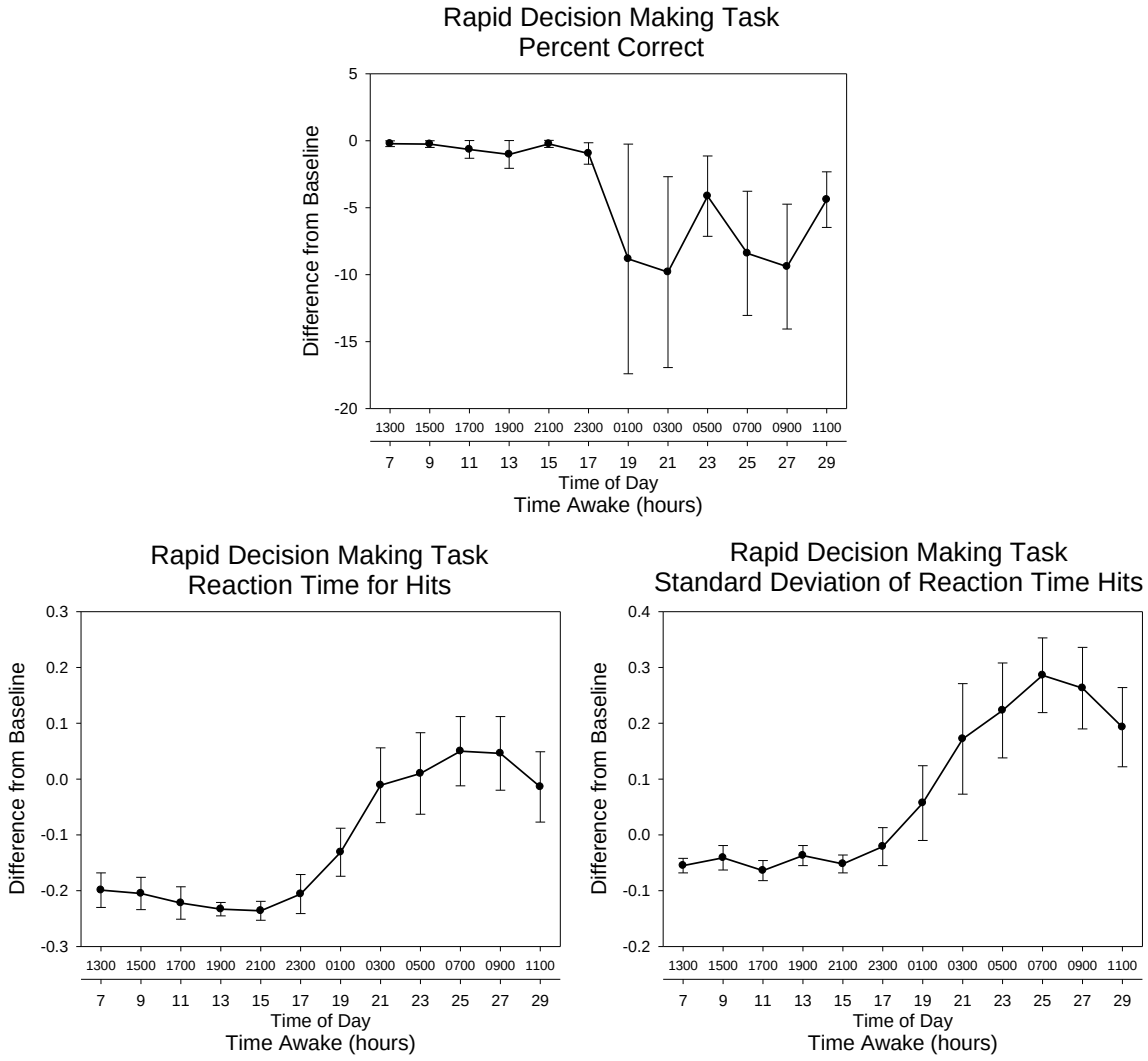

Figure 11. Session effects for Rapid Decision Making Task (means and sd)

3.4 Profile of Mood States (POMS) and Visual Analogue Scale (VAS)

The ANOVA analyzing the factors from the POMS indicated a significant session effect for Tension/Anxiety ($F(11,99) = 2.364$, $p = .012$), Vigor/Activity ($F(11,99) = 11.997$, $p < .001$), Fatigue/Inertia ($F(11,99) = 22.388$, $p<.001$), and Confusion/Bewilderment ($F(11,99) = 6.645$, $p<.001$). Further investigation into the session effects indicated a linear trend for Vigor/Activity, Fatigue/Inertia, and Confusion/Bewilderment ($p<.05$), with Tension/Anxiety showing a tendency in for this effect ($p=.067$). A quadratic trend was revealed for the Fatigue/Inertia and Confusion/Bewilderment factors ($p<.05$), and a cubic effect also occurred for the Vigor/Activity, Fatigue/Inertia, and Confusion/Bewilderment factors ($p<.05$). These effects are illustrated in Figure 12. Graphs for the non-significant factors are in Appendix A.

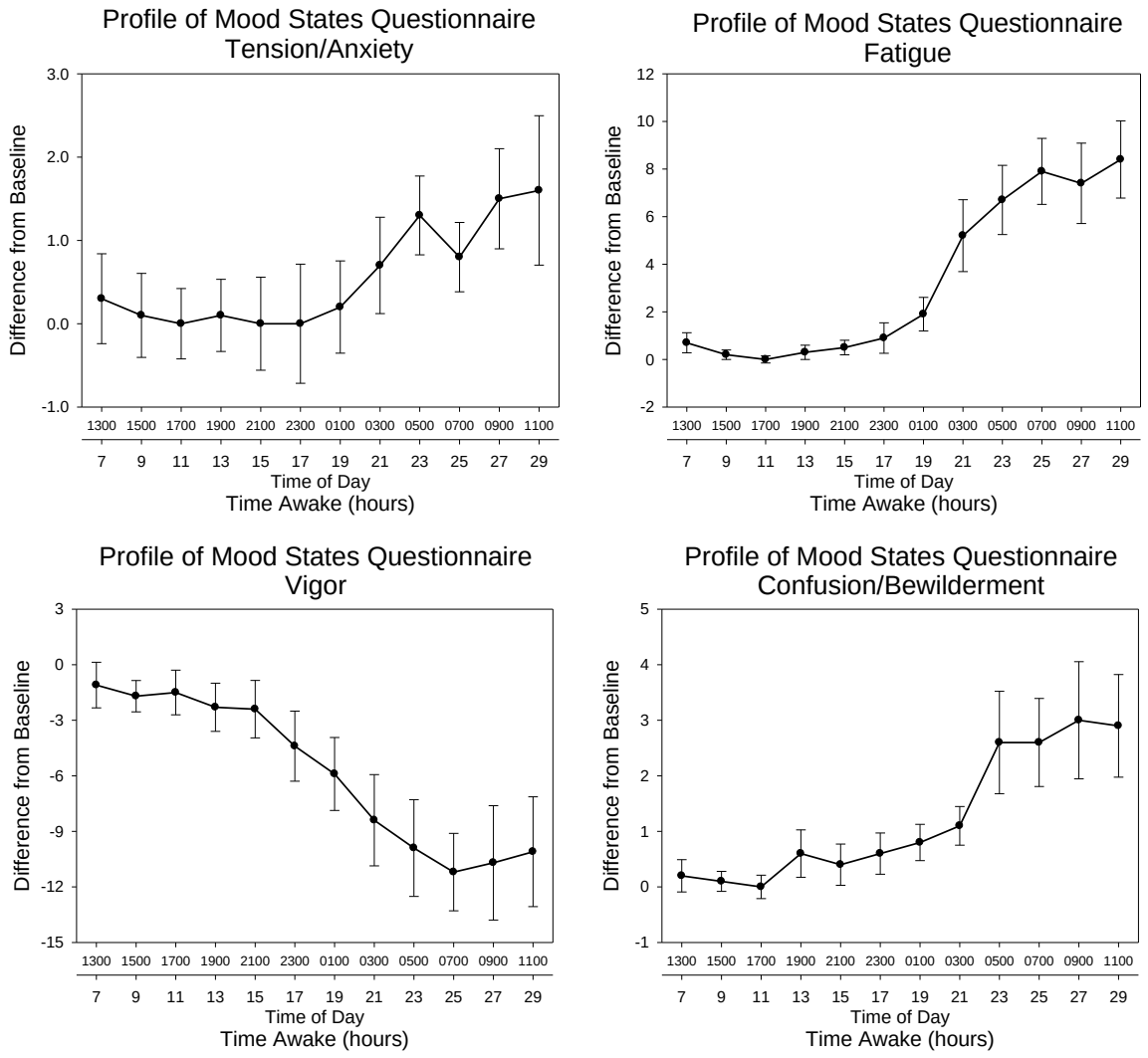

Figure 12. Session effects for Profile of Mood States (means and sd)

The VAS variables were analyzed with a repeated measures ANOVA which revealed a significant session effect for Alert ($F(11,99) = 11.762$, $p<.001$), Anxious ($F(11,99) = 2.018$, $p=.034$), Energetic ($F(11,99) = 14.802$, $p<.001$), Confidence ($F(11,99) = 4.229$, $p<.001$), Sleepy ($F(11,99) = 28.992$, $p<.001$), and Talkative ($F(11,99) = 6.454$, $p<.001$). Only Irritable and Jittery did not show a difference among the sessions ($p>.05$). Further investigation revealed significant linear and cubic trends for Alert, Energetic, Confident, Sleepy, and Talkative; Alert, Energetic, and Talkative also had a significant quadratic trend. Anxious did not indicate any significant trends. The effects of session on each of the variables are shown in Figure 13. Those factors not showing a statistically-significant effect are graphed in Appendix A.

3.5 Sternberg Working Memory task and brain activation

All 10 participants contributed fMRI data, however, one individual was left-handed, therefore, his fMRI data were not used for the correlations since handedness may alter brain activation. Therefore, the data set for the following analyses included 9 participants (8 men and 1 woman). A paired *t*-test was used to analyze the metrics obtained during the Sternberg Working Memory task performed during the MRI. The analysis showed a difference in percent correct as well as reaction time between the baseline scan and the 30-hrs awake scan ($t(9) = 2.528$, $p = .035$; $t(9) = -4.990$, $p = .001$, respectively). The means and standard errors are shown in Table 2.

Table 2. Means (sd) of Sternberg Working Memory test performance

	Baseline	30-Hrs Wakefulness
Percent Correct	98.61 (0.60)	93.06 (1.90)
RT	0.93 (0.50)	1.43 (0.08)

Areas of activation from the fMRI scans were calculated for global activation and global deactivation. Activation from the left dorsolateral prefrontal cortex (LDLPFC), the left posterior parietal cortex (LPPC), and the left ventrolateral prefrontal cortex (LVLPFC) was also calculated. Correlations between activation during the baseline and sleep-deprived fMRI scans and performance on the Sternberg Working Memory task (baseline and sleep-deprived) were computed. The results indicated significant correlations ($p<.05$) between percent correct and baseline global activation, LDLPFC, and LVLPFC. No significant correlations were revealed between the performance metrics and the activations seen after 30 hours of wakefulness. Tables for each of the correlation sets are provided in Tables 3 and 4 below. Graphic representations of the significant correlations are shown in Figure 14.

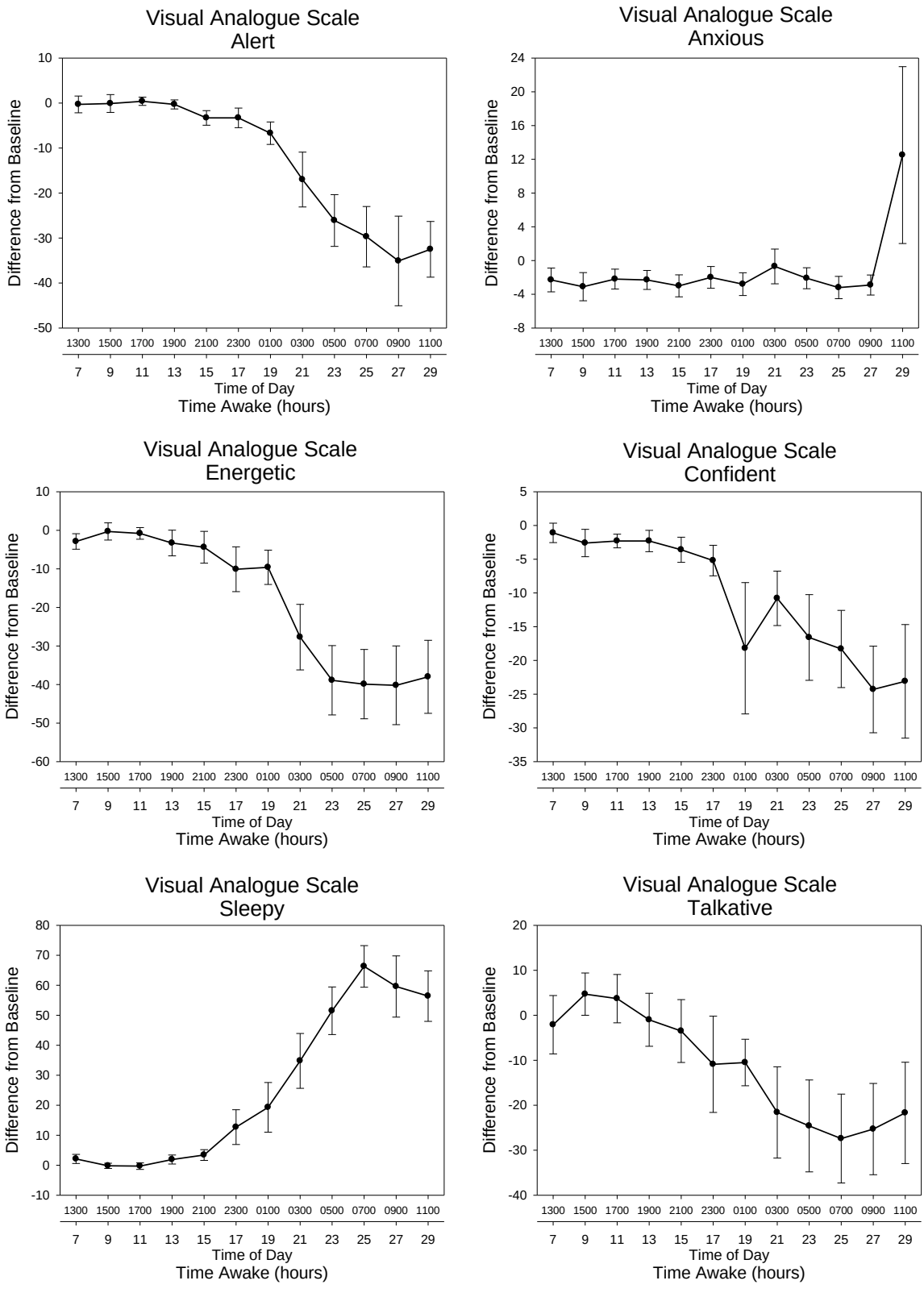

Figure 13. Session effects for Visual Analogue Scale (means and sd)

Table 3. Correlations between baseline fMRI activation and performance metrics on the Sternberg Working Memory test

	Percent Correct	Reaction Time
Global Activation	*.843	-.125
LDLPFC	*.834	-.361
LPPC	.635	-.040
LVLPFC	*.670	-.228
Global Deactivation	.526	-.374

* $p<.05$

Table 4. Correlations between fMRI activation and performance metrics on the Sternberg Working Memory test following 30 hours of wakefulness

	Percent Correct	Reaction Time
Global Activation	.093	.305
LDLPFC	-.438	-.357
LPPC	-.110	-.025
LVLPFC	.148	-.236
Global Deactivation	.054	.196

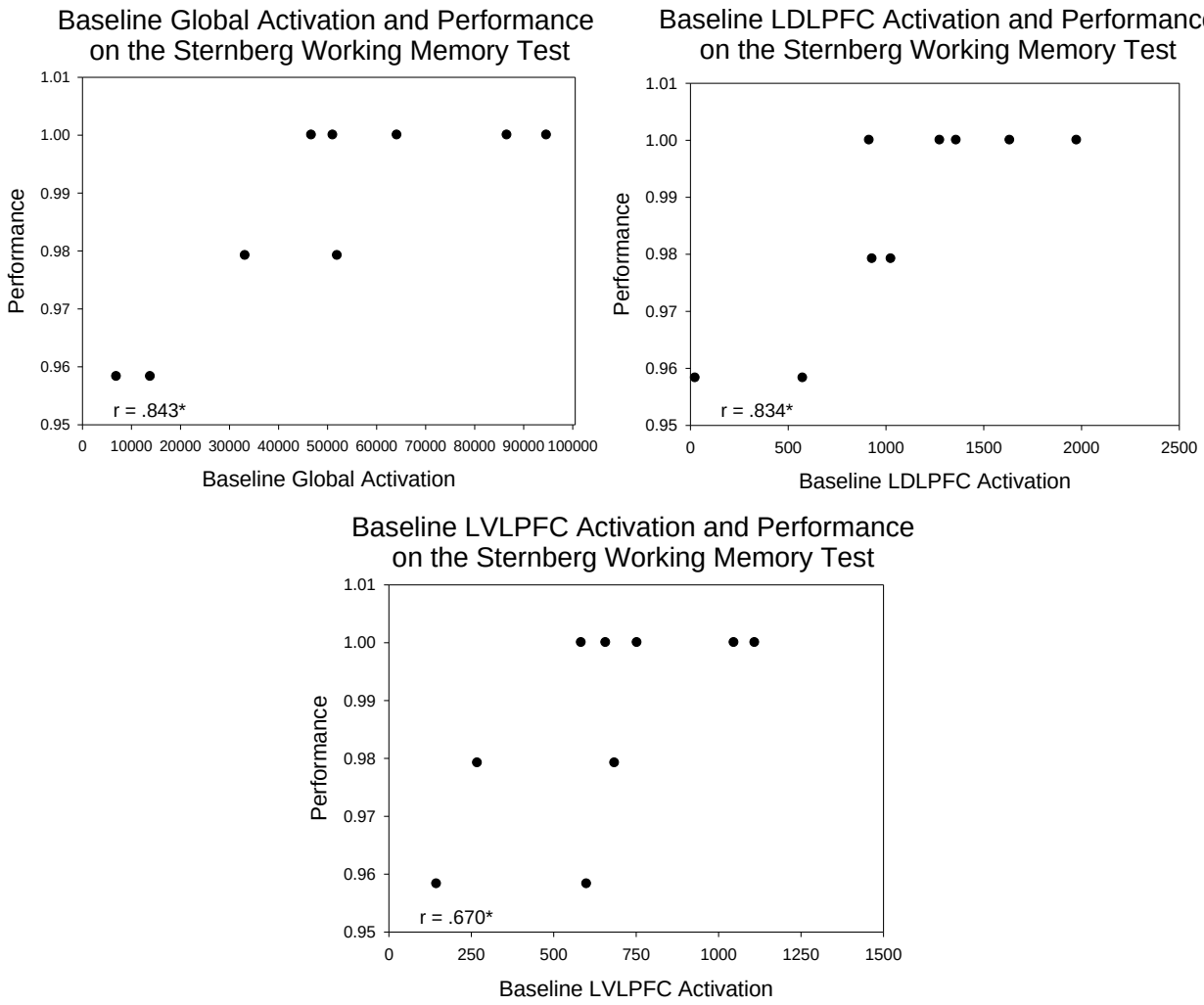

Figure 14. Correlations in baseline brain activation and performance on the Sternberg Working Memory Test

In order to determine the relationship between fMRI activation and performance decrements during 30 hours of wakefulness, the Spatial Working Memory task was selected since this test requires similar cognitive functions as does the Sternberg Working Memory Test. Metrics used for the correlational analysis from the Spatial Working Memory task were between errors, reaction time, and strategy. To obtain one measure to represent performance over the 30 hours of wakefulness, performance from each of the 12 sessions was converted to difference-from-baseline scores and then averaged across all the sessions. Correlations were then calculated on the averaged difference scores for between errors, reaction time, and strategy from the Spatial Working Memory task between both rested and sleep-deprived fMRI data. The only significant relationship was between the baseline LPPC activation and the average strategy score ($r = .722$, $p < .05$). No signification correlations were found between the performance metrics and the sleep-

deprived fMRI activation. The results are shown in Tables 5 and 6 below. The signification correlation is graphed in Figure 15.

Table 5. Correlations between baseline fMRI activation and averaged performance metrics on the Spatial Working Memory task

	Average Between Errors	Average Reaction Time	Average Strategy Score
Global Activation	-.156	-.182	.632
LDLPFC	-.217	.320	.590
LPPC	.143	.121	*.722
LVLPFC	.045	.505	.536
Global Deactivation	-.226	.245	.420

* $p<.05$

Table 6. Correlations between sleep-deprived fMRI activation and averaged performance metrics on the Spatial Working Memory task

	Average Between Errors	Average Reaction Time	Average Strategy Score
Global Activation	.204	-.112	.113
LDLPFC	.569	.021	.487
LPPC	.636	.029	.387
LVLPFC	.461	.045	.162
Global Deactivation	-.308	.492	.030

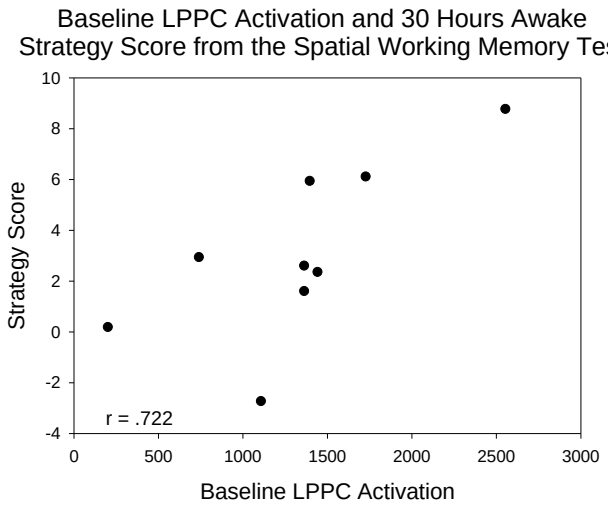

Figure 15. Correlation between baseline LPPC activation and the strategy score on the Spatial Working Memory test

The difference in brain activation between baseline and 30 hours awake was calculated; the differences were then correlated with the averaged strategy score from the Spatial Working Memory task. No significant correlations were found. All the correlations are presented in Table 7 below.

Table 7. Correlations between difference fMRI activation and averaged strategy score on the Spatial Working Memory task

Location	Correlation
Global Activation	-.432
LDLPFC	-.152
LPPC	-.328
LVLPFC	-.245
Global Deactivation	-.215

In order to determine how much change in brain activation occurred compared to the resting activation, correlations were calculated. The results indicated a significant negative correlation for global activation and LPPC (r = -.898, p=.001; r = -747, p=.021, respectively). There was a tendency for this relationship to occur with activation in the LDLPFC and LVLPFC (r = -.633, p = .067; r = -.608, p = .083, respectively). The relationships are shown in Figure 16 below.

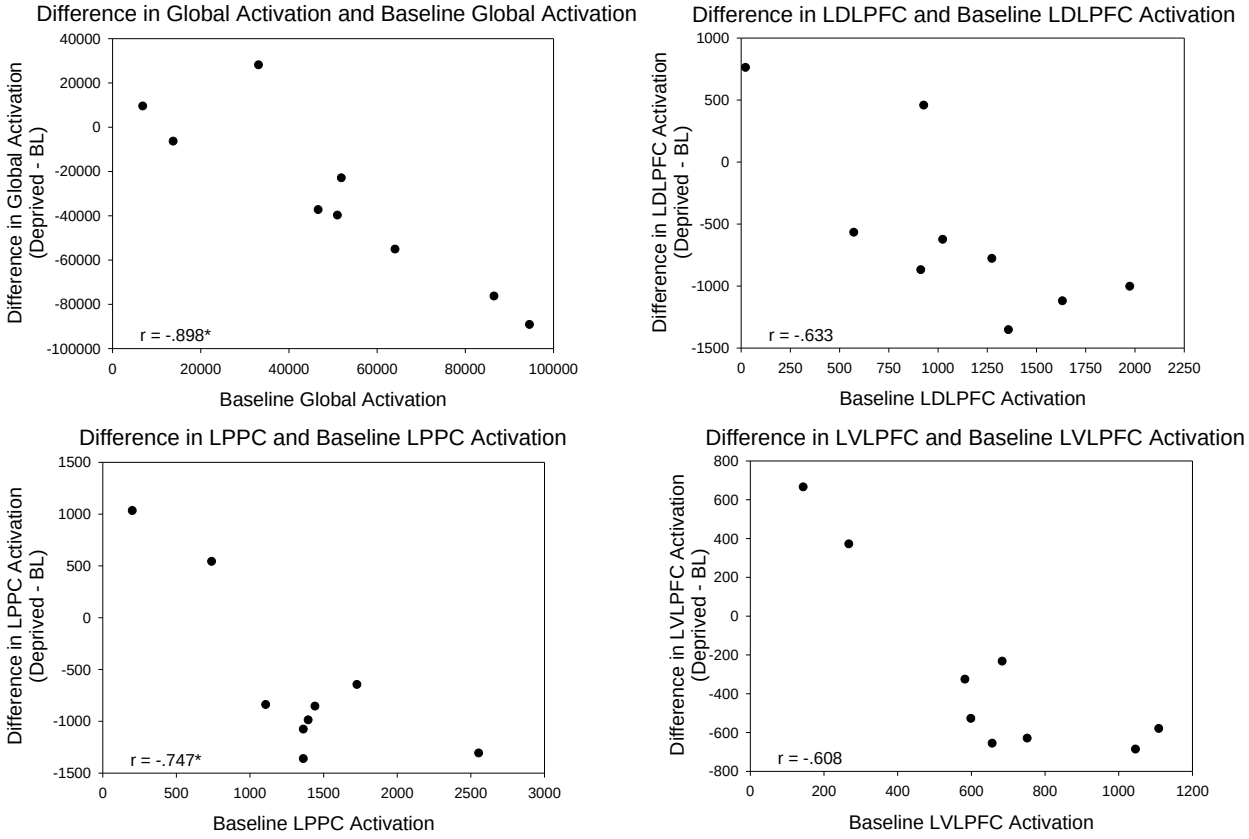

Figure 16. Correlations between resting brain activation and change in activation

3.6 Binary Detection task and brain activation

The Binary Detection task used to obtain additional fMRI data allowed the same set of correlational analyses to be computed with these data. Only 8 participants' data were used for these analyses; the woman participant was unable to see the task well enough to complete it, so she was not scanned.

A paired *t*-test was used to analyze performance obtained from the Binary Detection task completed during the fMRI scan. The analysis did not show a difference in percent correct between the baseline scan and the 30-hrs awake scan (p>.05). The means and standard errors for baseline and after 30 hours of wakefulness were 0.88, se = .05, and 0.79, se = .02, respectively.

Correlations between brain activation and deactivation during the Binary Detection task and performance on the Spatial Recognition task were computed. This test was selected due to its similarity to the Binary Detection. The metrics from the Spatial Recognition task used for the correlational analyses were percent correct and latency for correct response (correct reaction time). The averaged difference-from-baseline performance was calculated as before for this analysis.

Correlations were calculated between the averaged difference scores for percent correct and reaction time from the Spatial Recognition task and both rested and sleep-deprived fMRI data obtained during the Binary Detection task. None of the correlations between the performance metrics and the baseline or sleep-deprived fMRI activation were statistically significant. The results are shown in Tables 8 and 9 below.

Table 8. Correlations between baseline fMRI activation and averaged performance metrics on the Spatial Recognition test

	Average percent correct	Average Reaction Time
Global Activation	-.115	-.444
LDLPFC	-.081	-.273
LPPC	-.294	-.241
LVLPFC	-.206	-.353
Global Deactivation	.181	.041

Table 9. Correlations between sleep-deprived fMRI activation and averaged performance metrics on the Spatial Recognition test

	Average percent correct	Average Reaction Time
Global Activation	-.391	.610
LDLPFC	-.229	.083
LPPC	-.167	.490
LVLPFC	.103	.356
Global Deactivation	-.101	.136

The difference in brain activation between baseline and 30 hours awake were calculated; the differences were then correlated with the averaged percent correct and reaction time data from the Spatial Recognition task. None of the correlations were statistically significant ($p>.05$). All the correlations are presented in Table 10 below.

Table 10. Correlations between difference fMRI activation and averaged performance metrics on the Spatial Recognition test

	Average percent correct	Average Reaction Time
Global Activation	-.092	.620
LDLPFC	-.087	.275
LPPC	.128	.482
LVLPFC	.191	.427
Global Deactivation	-.202	.106

3.7 Magnetic Resonance Spectroscopy

The spectroscopy data set included 8 participants except for the basal ganglia which included only 7 participants. A paired *t*-test was used to evaluate the significance of changes in the metabolites in each brain region from resting wakefulness (RW) to 30 hours awake (SD). The *t*-test found significant differences between RW and SD for choline and lactate amounts at the basal ganglia ($t(6)=2.861$, $p=.029$; $t(6)=-2.980$, $p=.025$, respectively). NAA/creatine ratios at the basal ganglia did not differ between RW and SD ($p>.05$). None of the four metabolite levels in the pons and occipital lobes exhibited a difference between RW and SD ($p>.05$). The means and standard deviations for baseline and after 30 hours awake are shown in Figure 17.
To investigate the ability of MRS to predict individual levels of fatigue vulnerability, the baseline levels of choline, lactate, and NAA/creatine in the basal ganglia, pons, and occipital lobe were regressed onto the Spatial Working Memory task average strategy score using a linear regression model. None of the correlations were found to be significant between the strategy score and any of the metabolites in the basal ganglia or the occipital lobes ($p>.05$). However, lactate levels at baseline in the pons significantly correlated with the strategy score ($r = -.627$, $p = .048$), but levels of choline and the NAA/creatine ratio did not correlate with the strategy score ($p>.05$). The relationships are depicted in Figure 18 below.

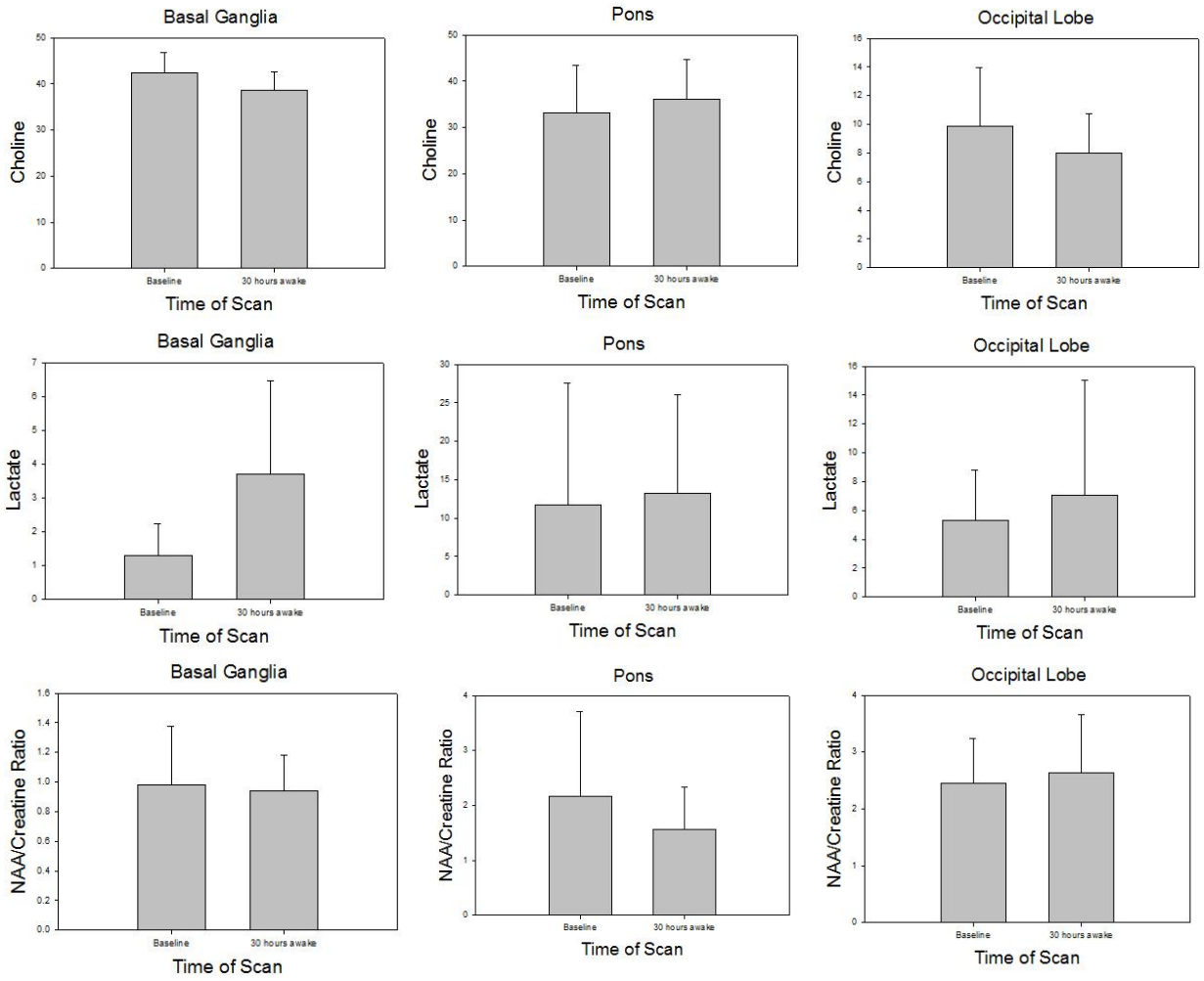

Figure 17. Choline, lactate, and NAA/creative levels of three volumes of interest (basal ganglia, pons, and occipital lobe) at RW and SD (means and sd)

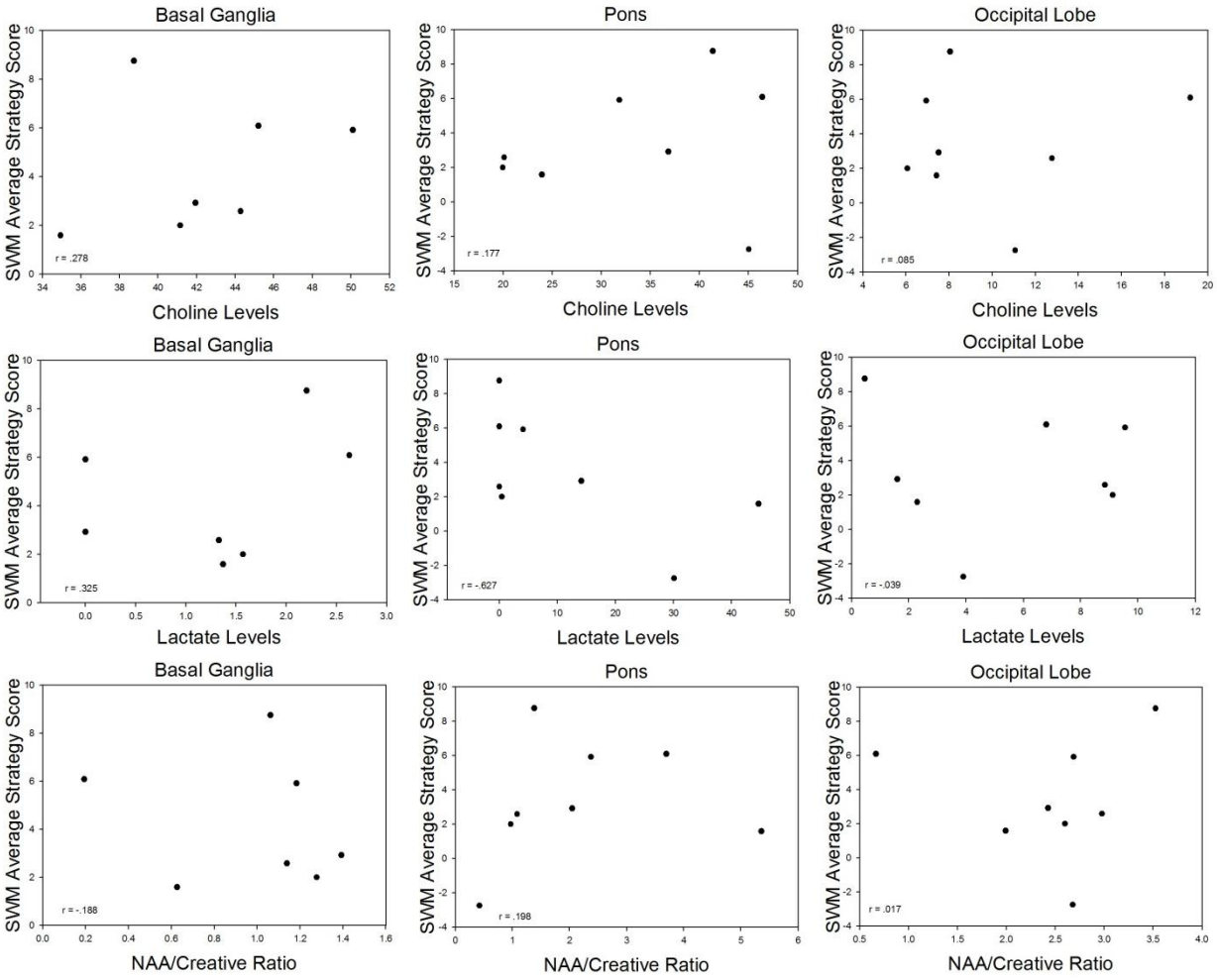

Figure 18. Analysis of baseline levels of choline, lactate, and NAA/creatine for the three volumes of interest (basal ganglia, pons, and occipital lobe) vs. Spatial Working Memory task average strategy score

To investigate the relationship between changes in metabolite levels in the brain and individual levels of fatigue vulnerability, the difference-from-baseline levels of choline, lactate, and NAA/creatine ratio in the basal ganglia, pons, and occipital lobe were regressed onto the Spatial Working Memory task average strategy score using a linear regression model. None of the correlations were found to be significant for any of the metabolite levels in the basal ganglia ($p>.05$). However, the difference in lactate levels in the pons and the NAA/creatine ratio in the occipital lobes were significantly correlated with the strategy score ($r = .646$, $p = .042$; $r = -731$, $p = .020$, respectively). The other metabolites in the pons and occipital lobes were not significantly correlated ($p>.05$). The relationships are shown in Figure 19.

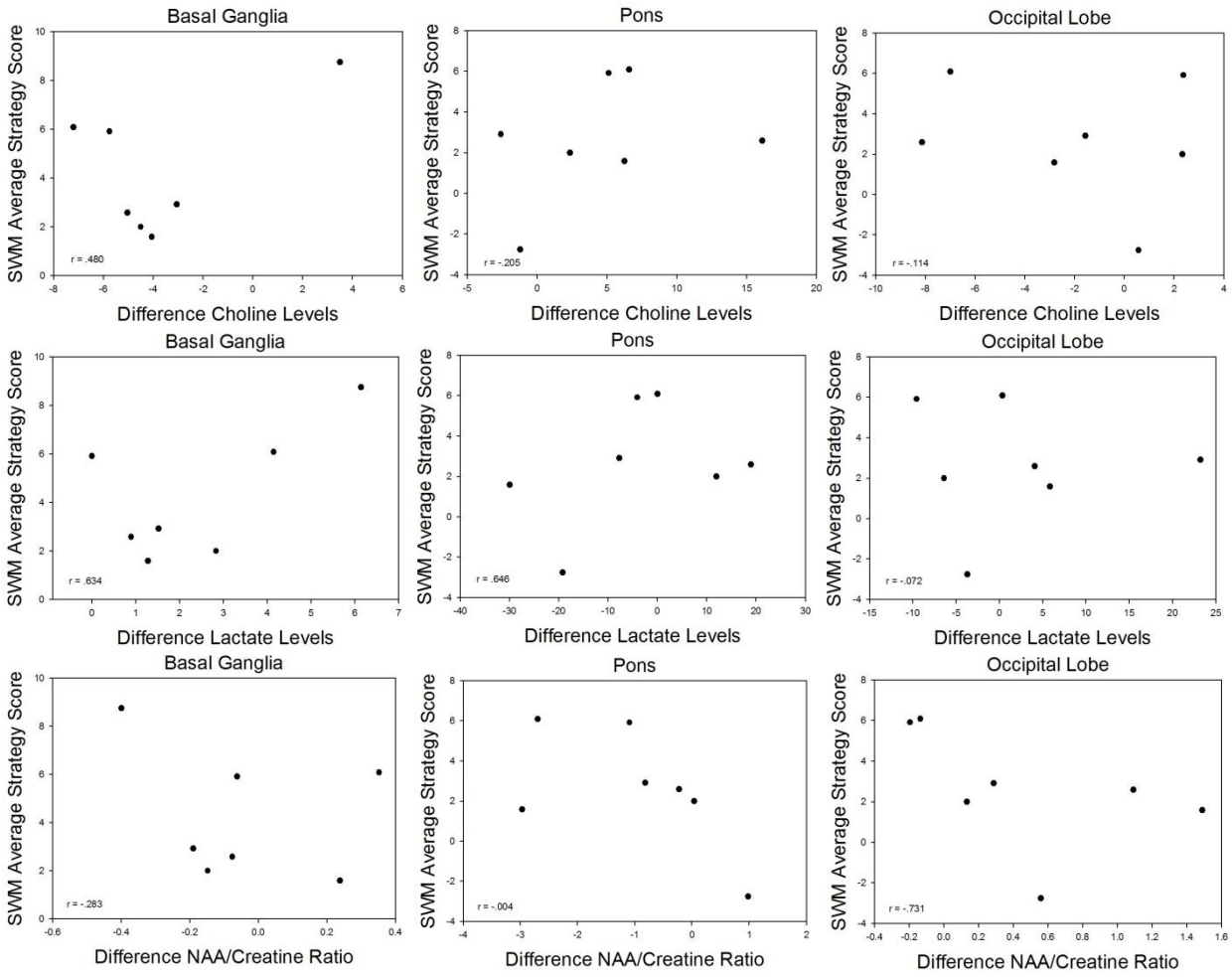

Figure 19. Analysis of difference-from-baseline levels of choline, lactate, and NAA/creative for the three volumes of interest (basal ganglia, pons, and occipital lobe) vs. Spatial Working Memory task average strategy score

3.8 Discussion

The purpose of the present study was to investigate the ability to predict susceptibility to the effects of sleep deprivation using fMRI. In addition, the study investigated the relationship between the cerebral metabolites N-acetyl-aspartate (NAA), choline (CHO), creatine (CRE), and lactate (LAC), and the mechanisms of vulnerability to fatigue. The results of the present study did not agree with previous results by Caldwell et al. (2005) and Mu et al. (2005) in that increased brain activation following 30 hours of wakefulness was positively correlated with decreases in performance. Therefore, increased brain activation indicated vulnerability to the effects of sleep deprivation rather than resistance. However, there were results which were relevant to findings by Chuah et al. (2006) which will be discussed.

The MR spectroscopy results of the present study found that in the basal ganglia CHO decreases and LAC increases with sleep deprivation. Contrary to the findings of Urrila (2006), significant

changes in metabolite concentrations were not found in the occipital lobe. This difference may be due to the small number of subjects included in the spectroscopy analysis (n=8). LAC levels in the pons at baseline were found to be negatively correlated with the Spatial Working Memory test strategy score, indicating that lower levels of LAC in the pons at baseline are predictive of fatigue vulnerability. The change in LAC between RW and SD in the pons was found to be positively correlated with Spatial Working Memory test strategy score, indicating that a greater increase in LAC in the pons during continuous wakefulness is indicative of fatigue vulnerability. Finally, the NAA/CRE ratio in the occipital lobe was negatively correlated with Spatial Working Memory test strategy score, indicating that a smaller increase (or greater decrease) in NAA/CRE in the occipital lobe is indicative of fatigue vulnerability.

3.8.1 Effects of sleep deprivation on cognitive performance and mood. As expected, individuals kept awake for 30 hours showed decrements in performance. In particular, performance on the PVT, both memory tasks and the gambling task from the CANTAB, and the rapid decision making task showed declines. The only performance task which did not show a decline over the wakefulness period was Stockings of Cambridge from the CANTAB. In addition, subjective mood also declined during the 30 hours of wakefulness as expected.

3.8.2 Correlations between rested brain activation and performance during continuous wakefulness. An unexpected result of this study was the correlation between resting brain activation, measured during the Sternberg Working Memory test, and performance on the Spatial Working Memory task performed during the continuous wakefulness period. The Spatial Working Memory task was chosen to correlate with brain activation due to the similarity in cognitive demand to the Sternberg Working Memory test. A significant correlation was found between the averaged strategy score on the Spatial Working Memory task and baseline fMRI activation in the LPPC. The present study indicated that those individuals who were most susceptible to the effects of sleep deprivation (indicated by a decline in performance during 30 hours of wakefulness) showed more baseline activation than did those less susceptible to the effects of continuous wakefulness. Similar results were seen in activation obtained during the Binary Detection test and performance on the Spatial Recognition test during continuous wakefulness, but none of the correlations were statistically significant, possibly due to the low number of participants contributing to the data set.

Possible reasons for the results in this study may be due to the theory posed by Chuah et al. (2006) who indicated that those individuals who are vulnerable to the effects of long hours of continuous wakefulness may require more resources to be able to perform as successfully as those who are not susceptible to sleep deprivation. A comparison of the activation from resting to sleep-deprived indicated that those with higher baseline (rested) activation (fatigue susceptible as indicated by performance) also had a greater reduction in activation after 30 hours of wakefulness, indicating fewer resources available when a stressor required more activation. This is consistent with those researchers who hypothesize that some individuals have a cognitive reserve which is activated when confronted with a stressor such as sleep deprivation, allowing them to pull from the reserve to perform better than those without reserve and therefore, succumb to the effects of the stressor (Van Dongen, 2005).

4.0 CONCLUSION

The present study sought to replicate previous studies in which brain activation, measured through fMRI, may identify those individuals who are susceptible to the effects of long hours of continuous wakefulness. While the present study did not replicated the findings of Caldwell et al. (2005) or Mu et al. (2005a), the results did indicate that fMRI data can identify those individuals who are susceptible to the effects of sleep deprivation. However, this study supported the hypothesis which suggests that individuals who perform poorly during long hours of wakefulness may not have the cognitive reserve necessary to resist the effects of a stressor such as sleep deprivation. It is clear that identification of individual variability in performance during sleep deprivation is still in an infancy stage and more research is necessary to determine whether fMRI can be a useful tool in identification of individuals who are resistant to the effects of long hours of wakefulness.

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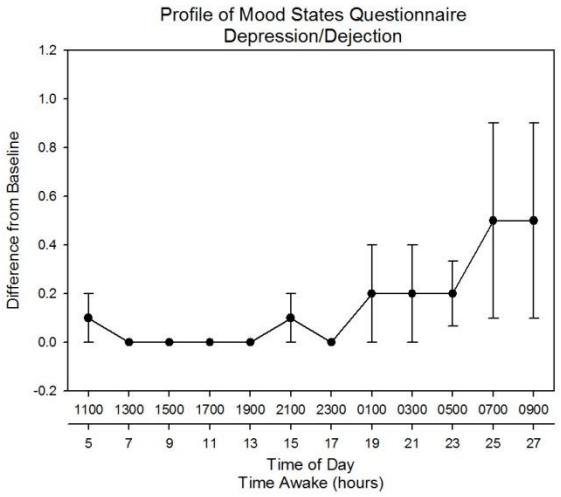
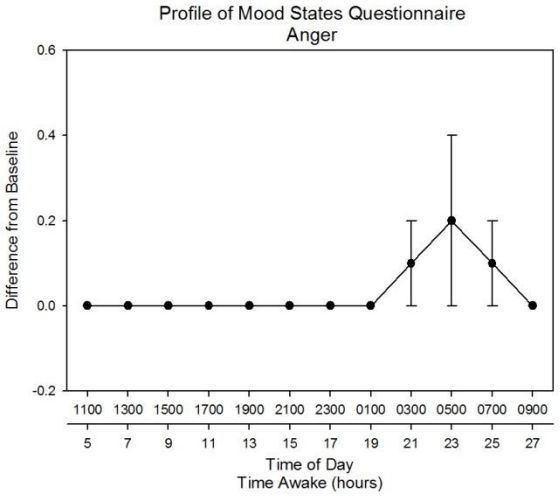
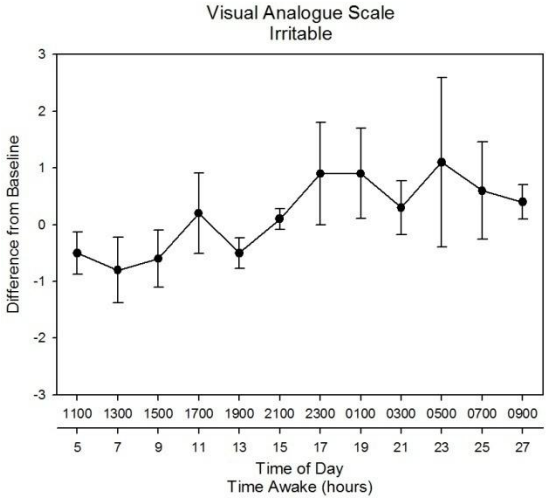
APPENDIX A

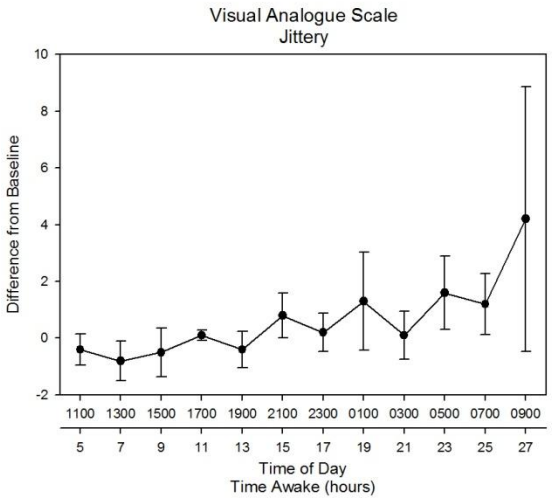
Additional graphs of POMS factors which did not have statistical significance across sessions





Additional graphs of VAS factors which did not have statistical significance across sessions





ABBREVIATIONS

AFRL	Air Force Research Laboratory
AUC	Area under the curve
BDT	Binary detection task
CHO	Choline
CRE	Creatine
EPI	Echoplanar imaging
fMRI	Functional Magnetic Resonance Imaging
FMRIB	Functional Magnetic Resonance Imaging of the Brain
FOV	Field of view
FRT	Fastest reaction time
FWHM	Full-Width Half-Maximum
KIC	Kettering Innovation Center
LAC	Lactate
LIP	Lipids
LDLPFC	Left dorsolateral prefrontal cortex
LPPC	Left posterior parietal cortex
LVLPFC	Left ventrolateral prefrontal cortex
MRS	Magnetic resonance spectroscopy
NAA	N-acetylaspartate
PVT	Psychomotor Vigilance Test
ROI	Region of interest
RT	Reaction time
RW	Resting wakefulness
SD	Sleep deprived
sd	Standard deviation
SRT	Slowest reaction time
SWMT	Sternberg Working Memory Test
UDRI	University of Dayton Research Institute
VOI	Volume of interest
WPAFB	Wright Patterson Air Force Base

ACRONYMS

ANOVA	Analysis of variance
CANTABeclipse	Cambridge Neuropsychological Assessment Battery: Eclipse
POMS	Profile of Mood States
WAM	Wrist activity monitor
VAS	Visual Analogue Scale